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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,328	DING ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-12 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-12 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included amendment to claims 1, 12, and 17, addition of new claims 18-19 and cancellation of claims 13 and 14, filed on 8/14/2006, are made of record. Claims 1-12 and 15-19 are now pending. Of which claims 2-5 were withdrawn from consideration as noted in the previous office action. Claims 1, 6-12 and 15-19 are under consideration.

In view of applicants' response, all 112 second paragraph rejections made in the previous office action have been obviated. In addition, 112 first paragraph the scope of enablement rejection of prodrug and process of claim 17 have been obviated. However, the amendment did not overcome, the 112 first paragraph scope of enablement rejection of hydrate or solvate as well as 102 and 103 rejections made in the previous office action. The amendment also necessitated additional grounds of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 18 is indefinite as it is not clear what are the variables embraced in the groups R^1, R^2, R^3 and Q. Without knowing these variables it is not possible examine this claim both for any missing essential elements and scope of enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-12 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Following apply.

1. Recitation of a condtional negative limitation in the R^1 definition of claim 1 clearly introduces new matter. The amended claim requires a condtional relationship that when X^3 is bond, the halo and haloalkyl substituents on the aryl or heteroaryl ring are not in meta position. Such a concept of conditional relationship has no support in the specification. This is a new matter.

2. Again, recitation of a condtional negative limitation in the R^3 definition of claim 1 clearly introduces new matter. The amended claim requires a condtional relationship that when X^3 is CR^4 and X^2 is N, then C_{6-10}aryl-C_{0-4}alkyl is C_{6-10}aryl-C_{1-4}alkyl. Such a concept of conditional relationship has no support in the specification. This is a new matter.

3. Similarly, recitation of a condtional negative limitation in the R^2 definition of claim 17 clearly introduces new matter. The amended claim requires a condtional relationship that when Q is fluoro, chloro, bromo and iodo, then R^2 is not halo, halo-substituted-C_{1-4} alkyl or halo-substituted-C_{1-4} alkyloxy. Such a concept of conditional relationship has no support in the specification. This is a new matter.

4. The newly added process claim 18 clearly introduces new matter. The process of claim 18 using R^3-ZnI is not disclosed in the pages 11-16. While support is provided for one specific example on page 21-22, applying the process to the genus as whole is not supported in the pages 11-16 wherein the scope of the process is clearly defined and does not include process of claim 18. Hence, the process claim 18 is clearly broadening the scope to genus from species.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 6-12 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making solvate or hydrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt solvate or hydrate thereof. Specification is not adequately enabled as to how to make hydrate of compounds of formula (I) Specification has no example of hydrate of the instant compounds. Specification on page 6 and 15 recites solvate or hydrate thereof but there is no enabling of such compounds.

The compound of formula I embrace pyrimidine compounds substituted with variable groups R^1, R^2, R^3 and R^4.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of alkyl., aryl heteroaryl, heterocyclyl, substituted aryl, heteroaryl, arylalkyloxy, arylalkylthio etc would result in hundreds of thousands of compounds. This is of course not the accurate number and the true number of compounds would far exceed this number of compounds. Thus the genus embraced in the claim 1 is too large and there is no teaching of any hydrate or solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of hydrate formation in general. The state of the art is that is not predictable whether solvates or hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is

not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to hydrates, which means a different solvent or even the moisture of the air that might change the stabile region of the hydrate. In the instant case of hydrate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to hydrate

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of hydrates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

2. **The predictability or lack thereof in the art:**

Hence, the solvate and hydrate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates and hydrates. There is no example of a solvate or

hydrate of instant compound. One hundred and twenty-six compounds were shown in the examples of the specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates or hydrates. Hence it is clear that merely bring the compound with solvent or water does not result in solvate or hydrate and additional direction or guidance is needed to make them Specication has no such direction or guidance.

4. **The presence or absence of working examples:**

There is no working example of any solvate or hydrate formed. The claims are drawn to hydrate, yet the numerous examples presented all failed to produce a solvate or hydrate or even hydrate. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates and hydrates of these compounds exist and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specication has no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate and hydrate of the compound of

formula I. As noted above, the genus embraces over million compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired hydrate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

This rejection is same as made in the previous office action but limited to currently pending claims. Applicants' traversal to overcome this rejection is not persuasive for reasons of record. As for the traversal, the following apply.

First of all, as stated above, specification has no showing the large genus of compounds of claim 1 formed hydrate or solvate. Over 126 compounds are disclosed, each of which have been in contact with water and solvent yet no solvate or hydrate formed. Thus bring a compound to water or solvent during recrystallisation or otherwise

did not lead solvate or hydrate. Hence, specification has no enablement for solvate or hydrate.

Secondly, contrary to applicants' assertion, there is no evidence in the non-patent literature that solvate or hydrate would form with any compound. It is unpredictable as noted in references cited by the examiner. Applicants have argued that interaction with water often results in hydrate but instant compounds have been in interaction with water and there is no evidence in the specification that they formed hydrate. As for Vippugunta, the article clearly states hydrate or solvate formation is no predictable. Applicants have inserted the word "predictably" but it is not there on page 15. In fact the next paragraph clearly states "mere presence of water in the system is not sufficient reason to expect hydrate formation...". As for Stahl et al. , a careful analysis would show that issue is not predictability but a finding that on third of compounds examined formed hydrate. Thus, two-third did not form hydrate and therefore there is no predictability of formation of hydrate or solvate. Again, the issue is does instant compound form hydrate or solvate not which pharmaceutical formed hydrate or solvate.

Hence, based on these considerations, the rejection is deemed as proper and is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-16 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer, does not reasonably provide enablement for treating any or all tumoral disease generically embraced in these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant method of use claims 15-16 are drawn to inhibiting Bcr-abl. Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of bcr-abl by the instant compounds, claims 15-16 are reach through treating any or all tumoral diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of bcr-abl, it is claimed that treating any or all tumoral diseases in general. The scope of the claims includes any or all tumoral diseases due to Bcr-abl inhibition including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of treatment of tumoral diseases would include treatment of various cancers including group consisting of lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal

region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have receptor tyrosine kinase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as tyrosine kinase inhibitor that would be useful for all sorts of tumoral diseases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The scope of the claims involves millions of compounds of claim 1 as well as the thousand of diseases embraced by the terms tumoral diseases.

Tumoral disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat tumoral diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed

invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Mass, R. D., Int. J. Radiation Oncology Bio. Phys.Vol. 58(3): 932-940, 2004 and Fabbro et al. Pharmacology & therapeutics 93, 79-98, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating tumoral diseases that require receptor tyrosine kinase inhibitory activity.

2) The state of the prior art: Recent publications expressed that the receptor tyrosine kinase inhibition effects are unpredictable and are still exploratory. See Mass et al. and Fabbro et al., cited above especially the concluding paragraph.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all tumors by the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the

degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all tumoral diseases and the state of the art is that the effects of tyrosine kinase inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace treatment of any or all tumoral diseases with large genus of compounds.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make

and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action but now limited to claims 15 and 16. Applicants' amendment to limit the method of use to leukemia did not overcome this rejection as applied to claims 15 and 16.

Claims 15 and 16 are reach through claims. Based on the mode of action of the instant compounds as inhibitor of Bcr-abl, the claims reach through in treating any disease for which there is no enabling disclosure.

Hence, this rejection is proper as applied claims 15 and 16 and is therefore maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Boykin et al., US 5,686,456 for reasons of record. To repeat:

Boykin et al. teaches several 2,4-substitutedpyrimidine compounds for treating Pneumocystis carnii , which includes instant compounds. See column 2, formula 1 and note the definition of various variable groups. Especially note when R_4 is hydrogen or

alkyl, R_5 is hydrogen, alkyl, halogen or alkoxy, with the given definition of other substituents, compounds taught by Boykin et al. include instant compounds. See entire document. See column 8-21 for various compounds, which include instant compounds.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive.

Contrary to applicants' urging, instant R^2 corresponds to R^5 of Boykin and therefore embraces the groups taught in Boykin et al. Furthermore, even with the proviso, the compounds taught would include instant compounds. Note the proviso of R^3 limit the choice of X^1 and X^2 not otherwise. Hence, this rejection is proper and is maintained.

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Carling et al., US 5,763,448 for reasons of record. To repeat:

Carling et al. teaches several pyrimidine compounds for treating schizophrenia which include instant compounds. See column 1, formula 1 and note the definition of A, Q, R^1 and R^2 groups. Especially note the definition of A, Q, R^1 and R^2 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Carling et al. therefore include instant compounds. See column 2-8 for further details of the invention. See column 9-11 for species of compounds, which include instant compounds.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive.

Contrary to applicants' urging, the rejection is proper to the extent it is applied to the elected subject matter, namely pyrimidine compounds, composition and method of use. The fact that the instant claims still embrace triazine (I^C), and pyridine (I^D), is irrelevant as only the elected subject matter was examined and the relevant art applied.

Again, as long as the reference teaches at least one of the isomeric pyrimidines (derived from variation in X^1 and X^2) the rejection is proper. In the instant case, contrary to applicants' urging, Carling et al., clearly teaches the pyrimidine depicted as I^B (i.e. when instant X^2 is N). More specifically, when instant X^2 is N, R^2 choices of reference include instant R^2 choices, Q choices include instant R^1 or L-R^3 wherein L is a bond and A choices include L-R^3 wherein L is a bond or R^1. Furthermore examples of Carling et al., include instant compounds. Hence, the reference is properly applied.

Hence, this rejection is proper and is maintained.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Cuccia et al., US 6,281,219 for reasons of record. To repeat:

Cuccia et al. teaches several pyrimidine compounds useful as insecticides, which include instant compounds. See column 1, formula 1 and note the definition of various variable groups. Especially note the definition of phenyl-X_1, phenyl-X_2 and R^1 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Cuccia et al. therefore include instant compounds. See column 2-17 for further details of the invention including the process of making which includes instant process. See column 18-23 for species of compounds, which include instant compounds.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive.

Contrary to applicants' urging, the rejection is proper to the extent it is applied to the elected subject matter, namely pyrimidine compounds, composition and method of use. The fact that the instant claims still embrace triazine (I^C), and pyridine (I^D), is irrelevant as only the elected subject matter was examined and the relevant art applied.

Again, as long as the reference teaches at least one of the isomeric pyrimidines (derived from variation in X^1 and X^2) the rejection is proper. In the instant case, contrary to applicants' urging, Cuccia et al. et al., clearly teaches the pyrimidine depicted as I^B (i.e. when instant X^2 is N). More specifically, R^1 choices of reference include instant R^2 choices, Phenyl-X_1 choices include instant R^1 or L-R^3 and Phenyl-X_2 choices include L-R^3 or R^1. Furthermore, examples of Cuccia et al., include instant compounds. Hence, the reference is properly applied.

The only variation is the substituents are permitted in the meta position in the reference while the instant amended claims exclude such a position by a proviso. As noted above, the proviso is deemed as new matter. If applicants' were to overcome the 112 new matter rejection then this rejection will be deemed as obviated

Hence, this rejection is proper and is maintained.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Wood et al., US 6,306,866 for reasons of record. To repeat:

Wood et al. teaches several pyrimidine compounds useful as insecticides, which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the

definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B, and R^1 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Wood et al. therefore include instant compounds. See entire document for further details of the invention. See column 6-14, especially Table I-III, for species of compounds, which include instant compounds.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive.

Contrary to applicants' urging, the rejection is proper to the extent it is applied to the elected subject matter, namely pyrimidine compounds, composition and method of use. Again, as long as the reference teaches at least one of the isomeric pyrimidines (derived from variation in X^1 and X^2) the rejection is proper. In the instant case, contrary to applicants' urging, Wood et al. et al., clearly teaches the both the isomeric pyrimidines (i.e. X^2 is N or X^1 is N). More specifically, referring to formula I of Wood and instant formula, when Z is N, the pyrimidine compound corresponds to instant pyrimidine wherein X^2 is N. The R^1choices of reference include instant R^2 choices, A-X choices include instant R^1 or L-R^3 and B choices include L-R^3 or R^1. Furthermore, examples of Wood et al., shown in Table I-III include instant compounds. Hence, the reference is properly applied.

Hence, this rejection is proper and is maintained.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheiblich et al., US 6,313,072 for reasons of record. To repeat:

Scheiblich et al. teaches several pyrimidine compounds useful as herbicides, which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B- R^3, R^1 and R^2 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Scheiblich et al. therefore include instant compounds. See column 2-11 for further details of the invention and process of making. See column 12-13, especially Table, for species of compounds, which include instant compounds.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive.

Contrary to applicants' urging, the rejection is proper to the extent it is applied to the elected subject matter, namely pyrimidine compounds, composition and method of use. Again, as long as the reference teaches at least one of the isomeric pyrimidines (derived from variation in X^1 and X^2) the rejection is proper. In the instant case, contrary to applicants' urging, Scheiblich et al. et al., clearly teaches the pyrimidine wherein X^1 is N. More specifically, referring to formula I of Scheiblich et al., and instant formula, the pyrimidine compound corresponds to instant pyrimidine wherein X^1 is N and X^2 is CR^4. The R^1choices of reference include instant R^2 choices, A-X choices include instant R^1 and B choices include L-R^3 wherein L is a bond. Furthermore, examples of Scheiblich column 12-13 include instant compounds. Hence, the reference is properly applied.

Hence, this rejection is proper and is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boykin et al., US 5,686,456 for reasons of record. To repeat:

Teachings of Boykin et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Boykin et al. teaches several 2,4-

substitutedpyrimidine compounds for treating Pneumocystis carnii, which include instant compounds. See column 2, formula 1 and note the definition of various variable groups. Especially note when R_4 is hydrogen or alkyl, R_5 is hydrogen, alkyl, halogen or alkoxy, with the given definition of other substituents, compounds taught by Boykin et al. include instant compounds. See entire document. See column 8-21 for various compounds which include instant compounds.

Boykin et al. differs in exemplifying not all compounds generically embraced in the compound of formula I.

However, Boykin et al. teaches equivalency of those compounds taught in column 8-21 with those generically recited in column 2

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Boykin et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive for reasons of record and those discussed in the above rebuttal of applicants' traversal.

In addition, if applicants were to obviate the 112 new matter rejections noted above, the proviso still does not obviate this rejection.

While said compound(s) doesn't anticipate the scope of instant claims in view of the proviso, they are very closely related, being positional isomers of compounds i.e. substituents in meta position of in the said phenyl ring of the reference vs other

positions in the instant claims. However, positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Engelhardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers.

Thus, it would have been obvious to one skilled in the art at the time of the invention was made to expect instant compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

Hence, this rejection is proper and is maintained.

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al., US 5,763,448 for reasons of record. To repeat:

Teachings of Carling et al. as discussed in the above 102 rejection is incorporated herein. Carling et al. teaches several pyrimidine compounds for treating schizophrenia, which include instant compounds. See column 1, formula 1 and note the definition of A, Q, R^1 and R^2 groups. Especially note the definition of A, Q, R^1 and R^2 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Carling et al. therefore include instant compounds. See column 2-8 for further details of the invention. See column 9-11 for species of compounds, which include instant compounds.

Carling et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula I shown in column 1.

However, Carling et al. teaches equivalency of those compounds taught in examples 1-5 with those generically recited for compound of formula I in column 1.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Carling et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive for reasons of record and those discussed in the above rebuttal of applicants' traversal.

In addition, if applicants were to obviate the 112 new matter rejections noted above, the proviso still does not obviate this rejection.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuccia et al., US 6,281,219 for reasons of record. To repeat:

Teachings of Cuccia et al. as discussed in the above 102 rejection is incorporated herein. Cuccia et al. teaches several pyrimidine compounds useful as insecticides, which include instant compounds. See column 1, formula 1 and note the definition of various variable groups. Especially note the definition of phenyl-X_1, phenyl-X_2 and R^1 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Cuccia et al. therefore include instant compounds. See column 2-17 for further details of the invention including the process of making which include instant process. See column 18-23 for species of compounds, which include instant compounds.

Cuccia et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula I shown in column 1.

However, Cuccia et al. teaches equivalency of those compounds taught in examples 1-39 with those generically recited for compound of formula I in column 1.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Cuccia et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive for reasons of record and those discussed in the above rebuttal of applicants' traversal.

In addition, if applicants were to obviate the 112 new matter rejections noted above, the proviso still does not obviate this rejection.

While said compound(s) doesn't anticipate the scope of instant claims in view of the proviso, they are very closely related, being positional isomers of compounds i.e. substituents in meta position of in the said phenyl ring of the reference vs other positions in the instant claims. However, positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Engelhardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers.

Thus, it would have been obvious to one skilled in the art at the time of the invention was made to expect instant compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

Hence, this rejection is proper and is maintained.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al., US 6306,866 for reasons of record. To repeat:

Teachings of Wood et al. as discussed in the above 102 rejection is incorporated herein. Wood et al. teaches several pyrimidine compounds useful as insecticides, which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B, and R^1 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Wood et al. therefore include instant compounds. See entire document for further details of the invention. See column 6-14, especially Table I-III, for species of compounds, which include instant compounds.

Wood et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula IA, IB and IB1 shown in column 3-4.

However, Wood et al. teaches equivalency of those compounds taught in examples 1-5 with those generically recited for compound of formula I in column 3-4.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Wood et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive for reasons of record and those discussed in the above rebuttal of applicants' traversal.

Hence, this rejection is proper and is maintained.

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheiblich et al., US 6,313,072 for reasons of record. To repeat:

Teachings of Scheiblich et al. as discussed in the above 102 rejection is incorporated herein.

Scheiblich et al. teaches several pyrimidine compounds useful as herbicides, which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B- R^3, R^1 and R^2 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Scheiblich et al. therefore include instant compounds. See column 2-11 for further details of the invention and process of making. See column 12-13, especially Table, for species of compounds, which include instant compounds.

Scheiblich et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula I shown in column 1.

However, Scheiblich et al. teaches equivalency of those compounds taught in examples 1-18 with those generically recited for compound of formula I in column 1.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Scheiblich et al

and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive for reasons of record and those discussed in the above rebuttal of applicants' traversal.

Hence, this rejection is proper and is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-12 and 15-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 57-72 of copending Application No. 10/270,030. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter namely aryl substituted pyrimidines embraced in the instant claims are also embraced in the copending application 10/270,030.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection is same as made in the previous office action. Applicants have differed addressing the rejection till the application is indicated as in condition for allowance.

The rejection is maintained.

Claim Objections

Pharmaceutical claim 11 is objected to as it lacks inert or acceptable carrier. In addition, it recites "tumors" which is inconsistent with the method of use claim 12. Limiting to "leukemia" will not be objected to. Also replacement of "animals" with "animal" is suggested.

Election/Restrictions

This application contains claims 2-5 drawn to an invention nonelected with traverse in Paper filed on 11/9/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

10/27/2006